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Immediate Versus Delayed Radical Prostatectomy: Updated Outcomes Following Active Surveillance of Prostate Cancer

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Abstract

Background: Biopsy progression on active surveillance (AS) for prostate cancer (PCa) often reflects failure of the initial biopsy to detect cancer present at enrollment. The risks for delayed treatment among men who progress on AS are not well defined.
Objective: To report outcomes for men who underwent surgery after AS compared to men who underwent immediate surgery and the influence of selection bias on this outcome.
Design, setting, and participants: AS-eligible (ASE) men who underwent radical prostatectomy (RP) after a median of 20 mo of AS were compared to ASE men who underwent RP within 6 mo of diagnosis. A subset of men on AS who underwent RP after upgrade to Gleason 3 + 4 was compared to matched controls with similar pretreatment biopsy features who underwent immediate RP.
Outcome measurement and statistical analysis: Rates of adverse pathology (upstaging, positive surgical margin, or Gleason upgrading) were examined. Logistic regression was used to determine associations between treatment subgroup and adverse pathology.
Results and limitations: Of 157 ASE men who underwent delayed RP after AS, 54 were upgraded to Gleason 3 + 4 before surgery. ASE men who underwent immediate RP had lower probability of adverse pathology than ASE men who underwent delayed RP (hazard ratio [HR] 0.34, 95% confidence interval [CI] 0.21–0.55). The rate of adverse pathology did not differ between immediate and delayed RP patients matched for pretreatment characteristics (HR 0.79, 95% CI 0.27–2.28). The observational design of this study is its main limitation.
Conclusions: When compared to men with similar pretreatment biopsy features, those who underwent delayed RP were not at higher risk of adverse pathology.
Patient summary: The oncologic safety of delayed treatment when indicated for men enrolled in active surveillance for prostate cancer is important. We found that men who underwent delayed surgery had similar outcomes to men who underwent immediate prostatectomy.

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1. Introduction

The widespread availability of prostate-specific antigen (PSA) testing has led to an increase in the detection of low risk prostate cancer (PCa) over the last two decades [1]. Active surveillance (AS), a management option for low-risk PCa that involves careful observation and treatment of men who appear to have more aggressive disease

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during follow-up, is currently a recommended treatment option for men with low-risk PCa in Europe and the USA [2,3]. However, widespread uptake of AS has been slow. Reported community usage rates range from 10% to 50% for men with PCa with very low clinical risk [4,5]. This may be because of both patient and provider fear of unrecognized aggressive disease that will progress if not treated immediately. The grade and extent of cancer are probably undersampled in a substantial proportion of men on surveillance, as 20–40% of men will have a higher Gleason score (GS) or cancer volume after enrolling in AS [6–9]. Whether a window for cure is missed during time spent on AS is controversial. Most prior reports have compared the surgical outcomes for patients who underwent radical prostatectomy (RP) after a period of AS (AS + RP) to those who met AS criteria and underwent immediate RP (IRP). This study design leads to a selection bias favoring the IRP group since the goal of AS is to avoid treatment until evidence of progression warrants intervention, and therefore patients with higher risk are selected for surgery. This was well demonstrated in a recent study using this design in which patients who underwent AS + RP had a higher risk of adverse pathologic features when compared to those who met AS criteria and underwent IRP [10].

Here we report updated outcomes for patients who underwent AS + RP in a large, prospectively followed AS cohort and compare them to two separate IRP cohorts. First, we compared those who underwent AS + RP to those who met AS criteria and underwent IRP. Second, to address the issue of selection bias among those undergoing AS + RP, we conducted a matched pair analysis of men who underwent AS + RP and men who underwent IRP, matched for their pretreatment biopsy features.

2. Patients and methods

2.1. Patient population

Men who underwent RP for PCa in the University of California, San Francisco (UCSF) Department of Urology between 1990 and May 2014 formed the study cohort. All patients consented to prospective data collection under supervision by the institutional review board. Patients who underwent surgery within 6 mo of diagnosis (first positive biopsy) made up the IRP group. The delayed RP group comprised those who enrolled in AS and subsequently underwent RP $\geq$6 mo after diagnosis. Strict criteria for AS eligibility were PSA $\leq$10 ng/ml, clinical stage T1 or T2 cancer, biopsy GS 2–6, biopsy cores $\leq$33% positive, and single core $\leq$50% positive.

2.2. Independent variables

Demographic data (age, race/ethnicity, relationship status), diagnostic PSA, prostate volume, PSA density, clinical T stage, GS, number of cores taken and percentage positive at diagnostic biopsy, Cancer of the Prostate Risk Assessment (CAPRA) clinical risk score (0–10), and surgical CAPRA-S (0–12) were collected [11,12]. Validated risk groups for both clinical CAPRA and CAPRA-S scores are low (0–2), intermediate (3–5), and high ($\geq$6).

2.3. Outcomes

The primary outcome was any adverse feature on surgical pathology, defined as Gleason upgrade to primary pattern 4 or 5 since last biopsy, extraprostatic extension (EPE), seminal vesicle invasion (SVI), presence of positive lymph nodes, or positive surgical margin (pSM). The secondary outcome was recurrence-free survival after RP. Recurrence events were biochemical failure, defined as two consecutive PSA increases $\geq$0.2 ng/ml or additional treatment at least 6 mo after RP.

2.4. Selection of controls

Two separate approaches were used to evaluate the immediate and delayed RP groups to ensure accurate findings. The first cohort was selected to evaluate patients with similar clinical characteristics at diagnosis. We updated the previous UCSF study by Dall'Era et al [13] with a larger cohort, comparing groups of men meeting strict eligibility criteria for AS who underwent immediate versus delayed RP (the ASE (active surveillance eligible) analysis) [13]. We compared a second set of men with similar characteristics right before surgery. A sub-group of surgical patients was matched on diagnostic year, age, PSA, and clinical T-stage (''matched pairs''). Matching techniques typically are used to pair cases with controls based on outcome. Instead, we used pair-matching to ensure that the exposure groups were as similar as possible. We then sought to eliminate progression bias between the treatment groups by matching men in the IRP group, who presented with biopsy GS 3 + 4 and underwent RP within 6 months, to the delayed RP group, who were diagnosed with Gleason 3 + 3, progressed to Gleason 3 + 4 upon repeat biopsy, and then underwent RP within 6 months of UG (the Matched analysis). Three IRP patients were matched to one delayed RP patient using the Greedy method [14].

2.5. Statistical analysis

Patient characteristics were compared between RP groups using t-test for continuous variables and Pearson chi-square for categorical variables. Logistic regression was used to evaluate associations between RP group and the outcome of any adverse pathology, adjusting for age, race, relationship status, clinical CAPRA score at diagnosis, PSA at diagnosis, PSAD (log) at diagnosis, and percentage of positive cores at last biopsy before surgery. Conditional logistic regression based on pair ID was used for the analysis of matched pairs, adjusting only for non-matching variables (race, relationship status, prostate volume, and percentage of positive cores at last biopsy before surgery.) Rates of recurrence-free survival were computed as Kaplan-Meier probabilities and compared by RP group with the log-rank test. Model covariates were assessed for inter-item correlations. A p-value $<$0.05 was considered significant. All analyses were performed using SAS 9.2 for Windows (SAS Institute, Cary, NC).

3. Results

Of 3372 men treated with RP during the study period, 241 men underwent delayed RP and 3131 underwent IRP. The cohort for the ASE analysis comprised 678 who met AS eligibility criteria, 521 (77%) from the IRP group and 157 (23%) from the delayed RP group (Fig. 1). Among the 157 men who initially met the AS criteria and underwent delayed RP, the median time on AS before surgery was 20 mo (range 6–148). The mean age at diagnosis was 60.6 yr (standard deviation 6.9) and median PSA at diagnosis was 4.9 ng/ml (interquartile range [IQR] 4.0–6.1). The median number of biopsy cores taken at diagnosis was 14 (IQR 12–16), and a median 13% of those cores contained cancer (IQR 8–21%). A median of two surveillance biopsies (range 1–10) were performed before RP. The median time from the last surveillance biopsy to RP was 4 mo (IQR 3–15) and the

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